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A Controlled Study of Longitudinal IQ Changes in Females and Males With Fragile X Syndrome

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The aim is this study is to compare the longitudinal changes in IQ scores of females and males with fragile X syndrome and controls and to assess the impact on IQ of molecular variations of the FMR-1 gene in males. Medical records from the child development unit at a university-affiliated children's hospital were retrospectively reviewed. Chart review yielded 35 males with fragile X (19 with a fully methylated full mutation, 9 with a mosaic pattern, and 7 with a partially unmethylated full mutation) 16 females with fragile X and a full mutation, 9 female controls, and 9 male controls who had repeated standardized IQ testing separated by 7 months to 13 years. The differences between the first and last IQ scores from the same IQ test were compared by t tests and subsequently by analysis of variance. Overall, a significant IQ decline was seen in 10/35 (28%) of fragile X males, 0/9 (0%) of control males, 6/16 (36%) of fragile X females, and 1/9 (11%) of control females. The initial t tests and analysis of variance showed a significant difference in IQ ($p = 0.02$) between fragile X males and control males but did not show a significant difference between males and females with fragile X syndrome or between fragile X and control females. When an analysis of covariance was carried out with the initial IQ as a covariable, a significant difference persisted between fragile X and control males, with a greater IQ decline in fragile X males. There were limitations in using the same IQ test. A comparison among the molecular subgroups of males yielded a significant IQ decline in 3/9 (33%) of mosaic males, 6/19 (32%) of fully methylated full mutation males, and 1/7 (14%) of partially methylated full mutation males. An analysis of covariance using the initial IQ and the intertest interval as covariables demonstrated significant differences between the fragile X molecular subgroups and the controls. Our findings show that a substantial percentage of both male and female fragile X patients and female control patients demonstrated significant IQ decline. There was a significant difference in the IQ change between fragile X and control males. There were no significant differences between fragile X and female controls. There were also significant differences in IQ decline among males with different molecular patterns compared with controls. Males with a mosaic pattern versus control males had the most significant decline of the molecular subtypes. Although the numbers were limited, there was no significant IQ decline in males with less than 50% methylation of the full mutation. This suggests that a small amount of FMR-1 protein production, which is often seen in males with less than 50% methylation, protects against significant IQ decline.

KEY WORDS: fragile X, IQ follow up, learning disabilities, molecular/clinical correlations, methylation

INTRODUCTION

The intellectual ability of individuals with fragile X is highly variable, ranging from normal IQ with learning disabilities to severely mentally retarded [Hagerman, 1991]. Mental retardation is seen more often in males, with more than 80% of affected males presenting with

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mental retardation versus 25–50% of females with the full mutation [Hagerman et al., 1992; Rousseau et al., 1991, 1994].

The FMR-1 gene defect has 2 main forms: premutation (ca. 50–200 CGG repeats) and full mutation (>200 repeats). Approximately 20% of affected males have been found to possess a mosaic form, with some cells having the premutation and others the full mutation [Rousseau et al., 1991, 1994]. Although 100% methylation of the full mutation is typical for affected males and females, some males show only partial methylation [Rousseau et al., 1994]. Studies have suggested that males who have minimal methylation of full mutations have higher cognitive abilities than males with a fully methylated full mutation [Loesch et al., 1993; McConkie-Rosell et al., 1993; Hagerman et al., 1994].

Over the last several years, there has been growing concern over decreasing intellectual abilities in males with fragile X as measured by standardized IQ testing [Lachiewicz et al., 1987; Dykens et al., 1989; Hagerman et al., 1989; Hodapp et al., 1990; Fisch et al., 1992]. A preliminary study of females with fragile X showed a similar trend [Fisch et al., 1994]. The decrease in IQ is not accompanied by a loss of intellectual milestones by history, however, and mental age has been shown to increase gradually with actual age until a plateau in adolescence [Lachiewicz et al., 1987; Hagerman et al., 1989]. The IQ decline is hypothesized to be a failure of individuals with fragile X to continue intellectual development at a rate that would be predicted by their early IQ scores and compared with those of their age-matched peers [Lachiewicz et al., 1987]. Deficits in abstract reasoning appear to be central to this decline [Hagerman et al., 1989]. Dykens et al. [1989] found steady growth in IQ until late childhood or early adolescence, when mental age would plateau and IQ scores decrease. They hypothesized that endocrine factors involved in the onset of puberty may be related to IQ decline.

Adaptive behaviors as assessed on the Vineland Adaptive Behavior Scales also decrease in males with fragile X versus controls [Dykens et al., 1993]. Specifically, males with fragile X are weak in socialization skills, which usually increase in severity after 10–12 years old. Neuroanatomical findings show a decrease in the volume of the superior temporal lobe region and an increase in the size of the lateral ventricles, which become more pronounced with age in males with fragile X, and these findings may be related to a decline in IQ [Reiss et al., 1994, 1995].

FMR-1 protein (FMRP) is thought to be an mRNA binding protein, and its function may be critical for maintaining cognitive abilities throughout childhood. Three males affected by fragile X syndrome, who were shown to express a limited level of FMRP, maintained their IQ within the nonretarded range into adulthood [Hagerman et al., 1994; Merenstein et al., 1994].

Fisch et al. [1992] hypothesized that differences in genotype may explain why some males with fragile X demonstrate an IQ decline and others do not. Studies addressing molecular variations as they relate to IQ, however, have been conflicting. Staley et al. [1993] presented evidence that, on average, males with a mosaic pattern had higher IQ scores and less IQ decline than males with a full mutation, whereas Rousseau et al. [1994] and deVries et al. [1993] did not find such differences. Hagerman et al. [1994] and Merenstein et al. [1995] also demonstrated an IQ difference between fully mutated males and mosaic males. In addition, an unusual DNA pattern, a minimally methylated full mutation, was found in 3 males, and this pattern was associated with higher cognitive functioning when compared with males with a fully methylated full mutation. This variant methylation pattern was associated with FMRP production and was not seen in retarded males with fragile X syndrome [Hagerman et al., 1994]. A similar DNA pattern was seen by Loesch et al. [1993], McConkie-Rosell et al. [1993], Merenstein et al. [1994], and Smeets et al. [1995] and always in association with high-functioning or normal-IQ males. Steyaert et al. [1995] reported several brother pairs with fragile X syndrome where at least 1 brother had a partially unmethylated full mutation and a nonretarded IQ.

Affected females are often cognitively similar to high-functioning, nonretarded fragile X males. Approximately 50% of females with the full mutation have cognitive deficits, with an IQ score that is on the borderline or within the mentally retarded range [Rousseau et al., 1991]. The remaining 50% have normal IQ, but most have significant learning disabilities [Rousseau et al., 1991; Mazzocco et al., 1993]. Recent studies of longitudinal changes in IQ scores for females with fragile X have shown mixed results. Fisch et al. [1994] found that the decline in IQ scores in 11 females was comparable to that observed in males. A recent study by Brun et al. [1995], however, demonstrated IQ decline in fewer females (29%) as compared with reports of males, and this was not significantly different from a control group of females.

The present study was done to compare the longitudinal changes in IQ scores of females and males with fragile X syndrome and a control group of females and males and to assess the impact on IQ of molecular variations of the FMR-1 gene in males, such as premutation/full mutation mosaicism and incomplete methylation variants. Because females with fragile X syndrome are less affected cognitively than males, the first expectation is that males with fragile X should demonstrate a greater decline in IQ score than females and controls. In addition, molecular variations in males, such as partial methylation, may protect against IQ decline.

SUBJECTS AND METHODS

Subjects in this study were found after a thorough chart review of all patients with fragile X syndrome who were seen at the Child Development Unit at The Children's Hospital in Denver and who had undergone a minimum of 2 identical standardized IQ tests that were separated by 7 months to 13 years. Sixty-nine patients were found who had repeated IQ testing on the same IQ scale. The fragile X population consisted of 51 patients who were positive for fragile X by cytogenetic testing in folate-deficient culture media. Cytogenetic expression ranged from 1 to 36% in the females and

from 0 to 66% in the males. In addition, 12 of the 16 females and all of the 35 males had undergone DNA testing with Southern blot analysis as described by Taylor et al. [1994a]. The remaining 4 females were in fragile X families, and they manifested typical physical features of fragile X syndrome, with cytogenetic expression ranging from 8 to 25%. Two of the 35 males who had 0% cytogenetic expression demonstrated less than 50% methylation of their fragile X full mutation, and the remaining males had the fragile X full mutation with 100% methylation. All the females and 19 of the males studied demonstrated a fully methylated full mutation, 9 males expressed a mosaic pattern, and 7 possessed a partially unmethylated full mutation.

Of the 69 patients in this study, 18 were in the control group including 9 females and 9 males who were seen in the Child Development Unit for development or behavior problems and had undergone repeated IQ testing by using the same scale. These patients were negative for fragile X on cytogenetic or DNA testing or had another diagnosis without features of fragile X syndrome. The range of diagnoses for female and male control patients included language delay, attention deficit hyperactivity disorder, obsessive/compulsive disorder, fetal alcohol syndrome, pervasive developmental disorder, and mental retardation. In addition, some individuals had specific genetic disorders, including Tourette syndrome, and 1 patient was mosaic for trisomy 18.

IQ tests included the Kaufman Assessment Battery for Children, the Stanford-Binet, and the Wechsler intelligence scales. The analyses conducted in this study compared individual changes in IQ score between the first and last test scores from the same IQ scale.

STATISTICAL ANALYSIS

Fifty-one patients with fragile X and 18 control patients were used in our statistical analysis. A 2 (group) $\times$ 2 (sex) factorial analysis of variance was employed to examine age at the first IQ test, the initial IQ score, and the intertest interval between the first and last IQ tests. Table I summarizes these variables. There was no significant difference between fragile X and control patients in age at the first IQ test ($p = 0.33$), the initial IQ score ($p = 0.94$), or the intertest interval between similar tests ($p = 0.18$). The means for age at first test, initial IQ, and intertest interval are shown in Table I. The differences in IQ change between fragile X patients and controls were significant. Results showed a positive group main effect for IQ change ($p = 0.02$).

Sixteen of the 51 (31%) fragile X patients and 1 of the 18 (6%) control patients showed a significant decline in IQ score ($p < 0.01$). More specifically, a significant IQ decline was seen in 10 of 35 (28%) fragile X males, 0 of 9 (0%) control males, 6 of 16 (36%) fragile X females, and 1 of 9 (11%) control females ($p < 0.01$) (Table II).

In t test comparisons among the 4 individual study groups, there was a significant difference in IQ change (IQ diff) from first to last test between males with fragile X and control males ($p = 0.01$); the initial IQ was also significantly different ($p = 0.001$). There was a significant difference between fragile X females and control females in intertest interval only ($p = 0.041$) and no sig-

TABLE I. Patient Profiles for the First and Last IQ Scores

	Control females	Fragile X females	Control males	Fragile X males (all)	Full methyl fraX males	Mosaic fraX males	Partial-methyl fraX males
Number	9.00	16.00	9.00	35.00	19.00	9.00	7.00
Mean IQ from first test	73.4 ± 19.8	82.3 ± 11.3	72.1 ± 9.6	63.7 ± 16.8*	58.42 ± 16.56	71.1 ± 18.05	72.0 ± 13.04
Mean age (years) at first test	8.7 ± 3.8	7.9 ± 3.5	13.0 ± 9.4	9.9 ± 9.3	9.7 ± 9.37	5.96 ± 1.71	9.43 ± 5.6
Mean interest interval (years)	2.9 ± 1.7	5.1 ± 3.3**	3.6 ± 1.9	3.6 ± 2.3***	4.38 ± 2.34	6.13 ± 3.06	5.28 ± 5.62
Mean IQ diff	−0.6 ± 8.4	−3.5 ± 13.7	1.89 ± 8.7	−8.0 ± 9.72****	−5.47 ± 8.8	−12.4 ± 11.42	−9.14 ± 1.79

* Males with fragile X had significantly lower initial IQ scores than control males ($p = 0.001$, t test) and fragile X females ($p = 0.001$, t test).
** Females with fragile X had significantly longer intertest intervals than control females, $p = 0.041$, t test.
*** The intertest interval was significantly different between females with fragile X and males with fragile X, $p = 0.04$, t test.
**** The IQ diff comparing first and last IQ scores was significantly different between males with fragile X and control males, $p = 0.01$, t test.

nificant IQ diff ($p = 0.56$). When comparing females with fragile X to males with fragile X, there was a significant difference in intertest interval ($p = 0.04$) and in initial IQ ($p = 0.001$) but no IQ diff ($p = 0.25$). Because of these differences, the initial IQ and the intertest interval are included in subsequent covariant analysis.

The analysis of covariance controlling for initial IQ and intertest interval also shows a significant difference between males with fragile X and control males for IQ diff ($p < 0.0001$) but not between females with fragile X and control females for IQ diff ($p = 0.76$).

To examine whether molecular variations in fragile X relate to changes in IQ between the first and last tests, the same analyses were used to compare the 3 groups of fragile X males (males with fully methylated full mutations, mosaicism, and partially methylated full mutations) and controls. An analysis of covariance using the initial IQ and intertest interval as covariables demonstrated a significant difference among the 3 molecular subgroups and the male controls ($p < 0.05$). In addition, the males with a mosaic pattern showed a more significant drop in IQ than males with the full mutation ($p < 0.05$).

Table III shows the results for the percentage of individuals in the 3 molecular categories who had a significant change in IQ. A significant IQ decline was seen in 3 of 9 (33%) mosaic males, 6 of 19 (32%) fully methylated full mutation males, and 1 of 7 (14%) partially methylated full mutation males ($p < 0.01$). However, there was no significant decline in IQ in the 3 males who had less than 50% methylation of the full mutation.

TABLE III. Changes (%) in IQ Scores for the 3 Subgroups of Fragile X Males and Control Males

Group	Decline	No change	Increase	Total
Fully methylated full mutation males	6 (32)	13 (68)	0 (0)	19
Mosaic males	3 (33)	6 (67)	0 (0)	9
Partially methylated full mutation males	1 (14)	6 (86)	0 (0)	7
Control males	0 (0)	8 (89)	1 (11)	9

DISCUSSION

We report the first controlled retrospective study of longitudinal changes in IQ scores in females and males with fragile X syndrome. The t tests and the subsequent analysis of covariance have demonstrated significant differences in IQ change between fragile X males and control males. The males with fragile X had more significant IQ decline than did the controls. The 3 molecular groups of males with fragile X syndrome also showed significant differences in IQ decline when compared with controls. There was no significant difference in IQ change, however, between females with fragile X and control females. This study utilized many of the female patients described by Brun et al. [1995] who also found no significant difference in IQ change between females with fragile X and control females.

Hay [1994] discussed the importance of using the same IQ scale in longitudinal studies because of significant differences in standardization between different scales. Comparing scores between identical scales rather than different IQ scales may allow for a better critical analysis of IQ change through a shorter period of time (such as midchildhood). Historically, we have found that eliminating patients who have not been retested with the same IQ scale shortens the intertest interval, decreases the number of patients eligible for such a study, and does not allow for a lifespan perspective in follow-up IQ studies. An expanded version of the study presented here included 54 males with fragile X, 19 male controls, 21 females with fragile X, and 21 female controls who had a longer mean intertest interval (mean of 6.9 years vs. present mean of 3.8 years) and were tested with different IQ scales that were compared with z scores [Wright-Talamante et al., 1995]. In this study, 31% of males with fragile X, 26% of control males, 33% of females with fragile X, and 29% of control females suffered a decline in IQ. Although there was still a significant difference between IQ decline in males with fragile X and male controls, this difference only emerged when an analysis of covariance was done with the initial IQ as a covariable [Wright-Talamante et al., 1995]. The present paper was limited to using only the same IQ scale, so there was a significant decrease in the number of patients, particularly in the controls, which diminished the previous finding of IQ decline in controls. This initial finding was surprising and suggests that control patients with attention deficits combined with language delays and hyperactivity are at risk for IQ decline in a fashion similar to males with fragile X syndrome.

Regarding the molecular variations of the FMR-1 gene in males, the mosaic patients demonstrated the most significant IQ decline as compared with the controls. Perhaps they are at greatest risk because their earlier cognitive abilities were higher than those with a fully methylated full mutation. The males with the partially methylated full mutation had the lowest proportion of patients with a significant decline (14%, 1/7 patients) compared with those with the fully methylated full mutation (32%, 6/19 patients) and those with the mosaic pattern (33%, 3/9 patients) (Table III). In previous studies, patients with a minimally methylated or unmethylated full mutation were able to maintain their IQ scores within the nonretarded range [Loesch et al., 1993; McConkie-Rosell et al., 1993; Hagerman et al., 1994; Merenstein et al., 1994; Smeets et al., 1995; Steyaert et al., 1995], which has been associated with a

TABLE II. Changes (%) in IQ Scores in Group × Sex

Group	Decline	No change	Increase	Total
Fragile X females	6 (36)	8 (50)	2 (13)	16
Control females	1 (11)	7 (78)	1 (11)	9
Fragile X males	10 (28)	25 (71)	0 (0)	35
Control males	0 (0)	8 (89)	1 (11)	9

detectable level of FMRP production [Hagerman et al., 1994; Merenstein et al., 1994; Smeets et al., 1995]. The percentage of partial methylation of a full mutation has a significant relation to the level of FMRP production, such that individuals with more than 50% methylation produce little or no protein [Taylor et al., 1994b]. Interestingly, the 1 male in the partially methylated full mutation group who showed a significant decline in IQ had more than 50% methylation of the full mutation. None of the males who had less than 50% methylation of the FMR-1 gene experienced an IQ decline, which is consistent with the data of Taylor et al. [1994b], which demonstrates that this subgroup of patients with fragile X is most likely to produce a limited level of FMRP. Males who are mosaic for the full mutation and premutation may not produce significant levels of FMRP or may not attain the threshold necessary to maintain or further develop cognitive abilities such as abstract reasoning skills. However, a recent study by Merenstein et al. [1995] evaluated a much larger patient number (218 males) with fragile X syndrome. They found that mosaic males in adulthood had a higher mean IQ (60.1) than males with a fully methylated full mutation (41.2) but a lower mean IQ than males with less than 50% methylation of their full mutation (88.2).

Females with fragile X did not demonstrate significant differences from controls in IQ change but did demonstrate significant differences from fragile X males in initial IQ and intertest interval. Because females produce a level of FMRP most likely related to their activation ratio [Abrams et al., 1994; Sobesky et al., 1995], they are more protected from IQ decline than are males with fragile X syndrome.

The first weaknesses of this study are the limited number of control subjects tested and retested with the same IQ scale (Table I) and the limited number of individuals with fragile X syndrome in each of the 3 molecular subgroups. This small number of control patients reflects the difficulty in finding individuals who are retested with the same IQ measure because different IQ scales are used at different ages. Second, the possibility of selection bias is certainly present because the patients were seen at the Child Development Unit in Denver for clinical reasons. This selects for more severely affected individuals, both with and without fragile X, than would be seen in a population study. The IQ changes in these study patients may be more dramatic than those observed in other clinical groups and are certainly more severe than those seen in the general population.

IQ decline in patients with variant molecular patterns warrants further study. The males that appear to be at the lowest risk for IQ decline are those with less than 50% methylation of the FMR-1 full mutation. Larger numbers of these individuals should be studied for IQ changes over time and how these changes might relate to FMRP expression. Technology has improved the methods for measuring FMRP, as has been described by Willemsen et al. [1995]. We conclude that a threshold of FMRP production may protect against significant IQ decline.

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